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TITLE: Process for coating stents

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Coating may be formulated by mixing one or more therapeutic agents with the coating **polymers** in a coating mixture. The therapeutic agent may be present as a liquid, a finely divided solid, or any other appropriate physical form. Optionally, the mixture may include one or more additives, e.g., nontoxic auxiliary substances such as diluents, **carriers**, excipients, stabilizers or the like. Other suitable additives may be formulated with the **polymer** and pharmaceutically active agent or compound. For example hydrophilic **polymers** selected from the previously described lists of biocompatible film forming **polymers** may be added to a biocompatible hydrophobic coating to modify the release profile (or a hydrophobic **polymer** may be added to a hydrophilic coating to modify the release profile). One example would be adding a hydrophilic **polymer** selected from the group consisting of polyethylene oxide, polyvinyl pyrrolidone, polyethylene glycol, carboxylmethyl cellulose, hydroxymethyl cellulose and combination thereof to an aliphatic polyester coating to modify the release profile. Appropriate relative amounts can be determined by monitoring the in vitro and/or in vivo release profiles for the therapeutic agents.

This Example describes the preparation of coated **stents** containing various

levels of **rapamycin** for in vitro drug release testing.

0.06 gms of **Rapamycin** was dissolved into 0.8 gms of 15% CAP/GLY solution in
1,1,2 TCE. The resulting coating solution contained 33.3% w/w drug on a dry,
solid-only basis. **Stents** were coated by the method described in Example 1 and
the coated **stents** were designated as `Std 33%`.

0.015 gms of **Rapamycin** was dissolved into 0.5 gms of 18% CAP/GLY solution in
1,1,2 TCE. The resulting coating solution contained 14.3% w/w drug on a dry,
solid-only basis. **Stents** were coated by the method described in Example 1 and
the coated **stents** were designated as `14%`

0.028 gms of **rapamycin** was dissolved into 0.5 gm of 18% CAP/GLY solution in
1,1,2 TCE. The resulting coating solution contained 23.7% w/w drug on a dry,
solid-only basis. **Stents** were coated by the method described in Example 1.
The dip-coated **stents** were spray coated with polymer-only solution as described
in Example 6. The final coated **stents** were designated as `24-TC%`

0.028 gms of **rapamycin** was dissolved into 0.5 gm of 18% CAP/GLY solution in
1,1,2 TCE. The resulting coating solution contained 23.7% w/w drug on a dry,
solid-only basis. **Stents** were coated by the method described in Example 1.
The dip-coated **stents** were spray coated with polymer-only solution as described
in Example 6;

0.06 gms of **rapamycin** was dissolved into 0.8 gm of 15% CAP/GLY solution in
1,1,2 TCE. The resulting coating solution contained 33.3% w/w drug on a dry,
solid-only basis. **Stents** were coated by the method described in Example 1.
The dip-coated **stents** were spray coated twice with .epsilon.-caprolactone-co-lactide (Cap/Lac) solution as

described in Example 4.
The final coated **stents** were designated as `33-TC%`.

0.06 gms of **rapamycin** was dissolved into 0.8 gm of 15% CAP/LAC solution in
1,1,2 TCE. The resulting coating solution contained 33.3% w/w drug on a dry,
solid-only basis. **Stents** were coated by the method described in example 1.
The dip-coated **stents** were spray coated twice with polymer-only solution as
described in Example 6 (except .epsilon.-caprolactone-co-lactide was used as
the copolymer). The final coated **stents** were designated as `33-C/L TC%`.

This example describes the results of testing the in vitro drug release of
rapamycin from coated **stent**.

Coated **stents** were prepared as described in Example 7 with varying
concentrations of **rapamycin** were tested for the in vitro release of **rapamycin**
into an aqueous ethanol solution. As is indicated in FIG. 7, the **stents**
denoted by the diamonds had a primer coating and a base coating that contained
rapamycin. The total weight of the coating and **rapamycin on the each stent** was
approximately 450 .mu.g and contained 33 percent by weight of **rapamycin**. The
coating was a copolymer of .epsilon.-caprolactone-co-glycolide (45:55 mole
percent) applied by dip coating. The squares represent data points for **stents**
having a primer coating and a base coating containing **rapamycin**. The total
weight of the coating and drug was approximately 450 .mu.g, which contained 14
percent by weight **rapamycin**. The coating material was also a copolymer of
.epsilon.-caprolactone-co-glycolide (45:55 mole percent) applied by dip
coating. The triangles represent data points for **stents** that had a primer
coating and a base coating containing **rapamycin**. A primer

coating and base
coating (.epsilon.-caprolactone-co-glycolide 45:55 mole percent) were applied
by dip coating the **stent**. A top coat of 200 .mu.g
(.epsilon.-caprolactone-co-glycolide 45:55 mole percent) was then applied using
an ultrasonic spray device. The total weight of the coating and **rapamycin** was
650-700 .mu.g, which contained 24 percent by weight **rapamycin**. The Xs
represent data points for **stents** that had a primer coat and a base coating
containing **rapamycin**. The primer coating and base coating
(.epsilon.-caprolactone-co-glycolide 45:55 mole percent) were applied by dip
coating the **stent**. A top coat of 100 .mu.g
(.epsilon.-caprolactone-co-glycolide 45:55 mole percent) was then applied using
an ultrasonic spray device. The total weight of the coating and **rapamycin** was
550-600 .mu.g, which contained 24 percent by weight **rapamycin**. The asterisk
represents data points for **stents** that was coated with a primer, a base coat
and two top coats. The primer coating and base coating
(.epsilon.-caprolactone-co-glycolide 45:55 mole percent) were applied by dip
coating the **stents**. A top coat of 100 .mu.g
(.epsilon.-caprolactone-co-glycolide; 45:55 mole percent) was then applied
using an ultrasonic spray device. The total weight of the coating and
rapamycin was approximately 550 .mu.g, which contained 33 percent by weight
rapamycin. The circles represent data points for **stents** that were dip coated
with .epsilon.-caprolactone-co-lactide (40:60 mole percent). The **stents** were
then top coated with an ultrasonic spray with approximately 100 .mu.g of
.epsilon.-caprolactone-co-lactide. The total coating weighed about 550 .mu.g
and contained 33 percent by weight **rapamycin**.

Each **stent** was placed in a 2.5 mL of release medium (aqueous ethanol; 15
percent by volume at room temperature) contained in a

13.times.100 mm culture tube. The tube was shaken in a water bath (INNOVA.TM. 3100; New Brunswick Scientific) at 200 rpm while maintaining ambient conditions. After a given time interval (ranging from 15 minutes to one day) the tubes were removed from the shaker and the respective **stents** carefully transferred to a fresh 2.5 ml Aliquot of release medium. The new tube was placed on the shaker and agitation resumed. A sample was removed from the aliquot, which had previously contained the **stent** and placed in a HPLC vial for determination of the **rapamycin** content by HPLC.

The goal of this study was to assess the rate of release of **rapamycin** from polymer-coated **stents** introduced in vivo into the coronary arteries of Yorkshire pigs. At various times after introduction of **stents,** the pigs were euthanized and the coronary arteries removed, the **stents** dissected free of the artery and analysed for **rapamycin** content using loading assay previously described. Through comparison with the amount of **rapamycin** contained on control, non-implanted **stents,** the in vivo rate of **rapamycin** release from the polymer coatings could be determined.

FIG. 7 illustrates a typical in vivo release curve for a **stent** coating consisting of 33% **rapamycin** in polycaprolactone-co-glycolide.

This preliminary study was conducted to assess the ability of **rapamycin** released from .epsilon.-caprolactone-co-glycolide copolymer-coated **stents** to inhibit intimal hyperplasia in vivo. Fourteen days after receiving **rapamycin**-loaded or control polymer coated **stents,** the male Yorkshire pigs were euthanized and the coronary arteries removed, the vessels

prepared for
histological evaluation and analysed for the amount of intimal growth. Through
comparison control metal **stents and stents** containing polymer only, the in vivo
ability of **rapamycin** to prevent neointimal growth could be determined.

As can be seen in Table 1, local delivery of **rapamycin** to injured coronary
arteries resulted in a significant (p<0.05) reduction in intima:media ratio
in the 166 .mu.g treatment group and a small but non-significant reduction in
the 32 .mu.g treatment group when compared with the polymer and bare metal
control groups. **Rapamycin** delivered from the GAP/GLY coating also resulted in
non-significant dose-related decreases in neointimal area in both the 32 .mu.g
and 166 .mu.g treatment groups. The percent diameter stenosis as assessed by
angiography was also significantly reduced in the 2 **rapamycin** treatment groups
when compared to the CAP/GLY group, although the reduction in this parameter
from the metal control was small and non-significant. Never-the-less, in this
preliminary 14 day study, these data suggest that local release of **rapamycin**
from a biodegradable hydrophobic polymer coating may be capable of limiting the
amount of neointimal proliferation which occurs as a result of **stent**
deployment.

TABLE 1

Angiography Intimal (mm.sup.2)	% Diameter Stenosis	B/A Ratio	Treatment	Histology Intima/ Media ratio	Area
0.90 .+-. 0.05	24.8 .+-. 3.9.sup.1	1.27 .+-. 0.82	Metal Control (n = 10)		
0.91 .+-. 0.04	4.15 .+-. 0.11	38.0 .+-. 4.0	CAP/GLY (n = 8)	1.32 .+-. 0.23	
0.75 .+-. 0.04	3.27 .+-. 0.11	21.6 .+-. 3.6.sup.1	CAP/GLY + 32 .mu.g **rapamycin** (n = 10)	1.23 .+-.	

0.04 0.16 0.03 CAP/GLY + 166 .mu.g 0.65 .+-. 2.87 .+-.
23.9 .+-. 2.3.sup.1
1.27 .+-. **rapamycin** (n = 8) 0.04.sup.1,2 0.31 0.05
.sup.1 p < 0.05
from CAP/GLY .sup.2
p < 0.05 from Metal Control All values are mean .+-.
sem. B/A ratio =
balloon to artery ratio, an index of the consistency of
stent expansion from
group to group

	Title	Current OR	Current XRef
1	Modified stent useful for delivery of drugs along stent strut	623/1.42	623/1.39
2	Process for coating stents	427/2.3	427/2.25; 427/2.28; 427/232; 427/235; 427/355

	Retrieval Classif	Inventor	S	C	P	2	3	4	5
1		Wright, Carol et al.	☒	☐	☐	☐	☐	☐	☐
2		Hossainy, Syed F. A. et al.	☒	☐	☐	☐	☐	☐	☐

	U	1	Document ID	Issue Date	Pages
1	☐	☐	US 6273913 B1	20010814	7
2	☐	☐	US 6153252 A	20001128	16

	Image Doc. Displayed	PT
1	US 6273913	☐
2	US 6153252	☐